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DOI:

[10.1002/14651858.CD012104](https://doi.org/10.1002/14651858.CD012104)

Document Version

Publisher's PDF, also known as Version of record

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Citation for published version (APA):

Lally, J., Tully, J., & Maccabe, J. H. (2016). Clozapine augmentation for treatment-resistant schizoaffective disorder. *Cochrane Database of Systematic Reviews*, 2016(3), [CD012104].
<https://doi.org/10.1002/14651858.CD012104>

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Clozapine augmentation for treatment-resistant schizoaffective disorder (Protocol)

Lally J, Tully J, MacCabe JH

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Clozapine augmentation for treatment-resistant schizoaffective disorder.

Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD012104.

DOI: 10.1002/14651858.CD012104.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	3
METHODS	3
ACKNOWLEDGEMENTS	10
REFERENCES	10
CONTRIBUTIONS OF AUTHORS	12
DECLARATIONS OF INTEREST	12
SOURCES OF SUPPORT	12

Clozapine augmentation for treatment-resistant schizoaffective disorder

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Editorial group: Cochrane Schizophrenia Group.

Publication status and date: New, published in Issue 3, 2016.

Citation: Lally J, Tully J, MacCabe JH. Clozapine augmentation for treatment-resistant schizoaffective disorder. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD012104. DOI: 10.1002/14651858.CD012104.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To systematically review the clinical effects, efficacy and safety of pharmacological augmentation for clozapine in treatment-resistant schizoaffective disorder.

BACKGROUND

Description of the condition

Schizoaffective disorder is a chronic and severe mental illness, with a prevalence of 0.5% to 0.8% in the general population (Malhi 2008). For many people it follows a relapsing and remitting course, with periods of remission, interspersed with florid psychotic episodes and concurrent mood symptoms, either mania, mixed or depressive episodes. The classification of schizoaffective disorder as a separate condition to schizophrenia and bipolar affective disorder remains controversial, but it retains its place in diagnostic classification manuals as a standalone condition (APA 2013), with outcomes somewhere between those of schizophrenia and bipolar affective disorder (Harrow 2000; Marneros 2001; Mancuso 2014; Tondo 2016).

Treatment-resistant schizoaffective disorder occurs in a minority of patients in which their response to antipsychotic medication

or mood stabilisers, or both, is suboptimal. For these people, this means that persistent psychotic symptoms with accompanying affective change (hypomanic/manic or mixed or depressive) is the predominant clinical presentation, with poor functioning despite adequate treatment with antipsychotic medication or mood stabilisers, or both. There is no consensual definition of treatment resistance in schizoaffective disorder, making it difficult to estimate the number of treatment-resistant schizoaffective patients, but clinical experience indicates that some people with schizoaffective disorder demonstrate suboptimal clinical response at some point in the longitudinal course of their illness (Mancuso 2014; Tondo 2016).

Treatment options are restricted, with clozapine the only drug with established efficacy in treatment-resistant schizophrenia (Kane 1988; Meltzer 1989; Wahlbeck 1999; Chakos 2001; McEvoy 2006), with emerging evidence for its effectiveness in treatment-resistant bipolar affective disorder (Li 2015), and it is similarly used in treatment-resistant schizoaffective disorder (McElroy 1991; Banov 1994; Ciapparelli 2003).

Description of the intervention

Clozapine has shown efficacy in treating acute mania, decreasing depressive symptoms and in overall mood stabilisation (Gitlin 2006; Li 2015). Clozapine is the medication of choice in treatment-resistant psychotic disorders including schizoaffective disorder, producing a clinically effective response in 50% to 60% of those with treatment-resistant schizophrenia (Meltzer 1989; Meltzer 1992). A large, uncontrolled body of literature suggests that clozapine can be considered as a treatment for refractory schizoaffective disorder and bipolar affective disorder, similarly to its use in treating schizophrenia (Frye 1998; Li 2015).

For the 30% of treatment-resistant schizophrenia patients who fail to respond to clozapine, there are no evidence-based effective treatments (Meltzer 1992; Cipriani 2009; Sommer 2012), with clozapine typically being augmented with different mood stabilisers and antipsychotic medication (Porcelli 2012; Sommer 2012). A similar strategy is used in the management of schizoaffective disorder (McElroy 1991; Ciapparelli 2003).

We will define augmentation as the coadministration of different classes of medications or alternative antipsychotic medications to augment clozapine effectiveness. For example this might refer to the coadministration of first generation antipsychotics (FGAs) or second generation antipsychotics (SGAs), or mood stabilisers, antidepressants, or benzodiazepines, rather than add on therapies to treat adverse effects of clozapine treatment.

Mood stabilisers are medications which are effective in the acute treatment of manic symptoms or depressive symptoms, or both, and the prevention of manic or depressive symptoms. We have included here, as mood stabilisers, medications that preferentially act on and prevent relapse to the affective poles of the schizoaffective illness spectrum (e.g. mania or depression, without ill effect on the other) (Ketter 2002; Bauer 2004).

How the intervention might work

The exact mechanism of action of antipsychotics and mood stabilisers in schizoaffective disorder and other psychotic disorders is unknown. Mood stabilisers act on a diverse range of molecular and cellular targets and are thought to cause a range of direct effects on neural transmission, as well as downstream effects on neural and synaptic plasticity. Clozapine and other antipsychotic medications are thought to have mood-stabilising effects through their central dopamine and 5-HT_{2A} actions. The mechanism of clozapine as an antipsychotic of superior efficacy, and as a mood stabilising agent remain unclear. Clozapine has affinity at multiple neurotransmitter receptors in the brain, which may potentially mediate its efficacy, including dopamine (D₁, D₂, D₄), serotonin (5HT_{2A}, 5HT_{2C}, 5HT₆, 5HT₇), muscarinic (M₁, M₂, M₃, M₄, M₅) and adrenergic (alpha-1 and alpha-2) receptors (Miyamoto 2012). Other antipsychotic medications interact with some or all of these same receptors contributing to potential mechanisms

of efficacy as antimanic, antidepressant and mood stabilisation agents. D₂ receptor antagonism is thought to mediate anti-manic effects of antipsychotics (Cipriani 2011). Partial agonist activity at 5-HT_{1A} receptors (which most SGAs have) may contribute to their efficacy against depression, as well as negative symptoms of schizophrenia (Miyamoto 2012). Antagonism at 5-HT_{2C} receptors is reported to aid antidepressant action in SGAs (Jensen 2010). Antagonism at 5-HT₆ and 5-HT₇ receptors has been postulated to aid antidepressant effects (Nikiforuk 2015).

Lithium carbonate and anticonvulsant medications, such as sodium valproate and lamotrigine, function as mood-stabilising agents. Lithium carbonate broadly acts to stabilise neuronal activities, support neural plasticity, and provide neuroprotection (Jope 1999; Malhi 2013). It functions to modify neurotransmission, reducing excitatory (dopamine and glutamate), but increasing inhibitory (gamma-aminobutyric acid (GABA)) neurotransmission; modulating signalling linked to neural plasticity, including acting on cyclic AMP-dependent kinase, and protein kinase C; modulating second-messenger systems and gene expression; and having a neuroprotective effect by increasing proteins such as brain-derived neurotrophic factor and reducing oxidative stress (Jope 1999; Malhi 2013). Anticonvulsant mood stabilisers share similarities as well as differences with lithium, in their mechanism of action. They act to modulate regulatory and inhibitory neurotransmission, signal transduction and gene expression, and with possible neuroprotective effects (Cipriani 2011; Cipriani 2013). However, it remains unknown how these medications work in combination with clozapine in treatment-resistant schizoaffective disorder.

Why it is important to do this review

It is not possible at present to make reliable suggestions for the choice of the best augmentation strategy in people with schizoaffective disorder resistant to clozapine. This is due to the lack of clear guidelines about this difficult therapeutic challenge. A Cochrane review has already been published to assess the efficacy and safety of clozapine augmentation with other antipsychotic medication in people with treatment-resistant schizophrenia (Cipriani 2009). In schizoaffective disorder treatment, available data are almost exclusively provided as sub-group analyses from schizophrenia trials (Marneros 2001). In relation to the pharmacotherapeutic management of clozapine-refractory schizoaffective disorder, the literature is dominated by case studies and open label trials. Hence from a clinical perspective, very real questions arise about the best evidence-based treatments in this disorder, questions which become more challenging to answer in those with a clozapine-refractory illness (as for example, there may need to be a greater consideration for augmenting clozapine with mood stabilizers). As a result there is a need for this review to determine the most efficacious and well-tolerated treatments in clozapine-resistant schizoaffective disorder.

OBJECTIVES

To systematically review the clinical effects, efficacy and safety of pharmacological augmentation for clozapine in treatment-resistant schizoaffective disorder.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. If a trial is described as 'double blind' but implies randomisation, we will include such trials in a sensitivity analysis ([Sensitivity analysis](#)). If their inclusion does not result in a substantive difference, they will remain in the analyses. If their inclusion does result in important clinically significant but not necessarily statistically significant differences, we will not add the data from these lower quality studies to the results of the better trials, but will present such data within a subcategory. We will exclude quasi-randomised studies, such as those allocating by alternate days of the week. Where people are given additional treatments within the treatment groups, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the augmentation agent that is randomised.

Types of participants

Adults (18 years or more), however defined, with schizoaffective disorder by any means of diagnosis who remain resistant to clozapine treatment. We will include trials with a mix of diagnosis, including those where schizoaffective disorder is not in the majority. We will include such mixed-diagnosis trials only if trial data relating to those individuals with schizoaffective disorder are available.

We are interested in making sure that information is as relevant to the current care of people with schizoaffective disorder as possible so propose, where possible, to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and as to whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Any pharmacological intervention at any dose or route of administration whose primary aim is to augment clozapine in treatment-resistant schizoaffective disorder, e.g.

- Clozapine plus another antipsychotic medication

- Clozapine plus a mood stabiliser
- Clozapine plus an antidepressant medication
- Clozapine plus other treatments

We will investigate the following in trials: comparing clozapine plus augmentation drug versus clozapine alone, or clozapine plus augmentation drug versus augmentation drug alone, or placebo or any comparator.

Types of outcome measures

If possible, we will divide outcomes into short term (less than 3 months), medium term (up to 6 months) and long term (longer than 6 months). For any outcome assessed more than once in a particular term, we will extract data for each timepoint.

Primary outcomes

1. Mental state

1.1 Clinically important response in psychotic or affective symptoms, as defined by each of the studies (short term)

2. Service utilisation

- 2.1 Hospital admission, re-admission, or both
- 2.2 Days in hospital

Secondary outcomes

1. Leaving the study early

2. Global state

- 2.1 Average endpoint score or change score in global state
- 2.2 Clinically important response on global state, as defined by each of the studies

3. Mental State

- 3.1 Average endpoint score or change score in psychotic or affective symptoms
- 3.2 Clinically important response in specific symptoms, as defined by each of the studies

3.2.1 Positive symptoms

3.2.2 Negative symptoms

3.2.3 Manic symptoms

3.2.4 Depressive symptoms

3.3 Average endpoint score or change score in specific symptoms, as defined by each of the studies

3.3.1 Positive symptoms

3.3.2 Negative symptoms

3.3.3 Manic symptoms

3.3.4 Depressive symptoms

3.4 Recurrence of any affective or psychotic episodes - as measured by institution of additional treatment for affective or psychotic episode and time to institution

4. Adverse events: numbers of participants experiencing

- 4.1 Blood dyscrasias such as neutropenia or agranulocytosis
- 4.2 Metabolic adverse effects (including weight gain, dyslipidaemia and glucose dysregulation)
- 4.3 Extrapyrarnidal adverse effects
- 4.4 Gastrointestinal side effects: constipation, nausea, vomiting, dyspepsia
- 4.5 Central nervous system side effects: tremor, sedation, ataxia, cognitive impairment.
- 4.6 Cardiovascular adverse effects: tachycardia, QTc prolongation, hypertension or hypotension, myocarditis or cardiomyopathy

5. Other adverse effects

- 5.1 General and specific effects (including deaths by suicide or natural causes)
- 5.2 Average endpoint or change scores in adverse effects
- 5.2 Mortality due to agranulocytosis or haematological adverse effects
- 5.3 Mortality due to myocarditis or cardiovascular adverse effects
- 5.4 Rates of deliberate self-harm

6. Service utilisation outcomes

- 6.1 Days in hospital

7. Economic outcomes

- 7.1 Direct costs of care
- 7.2 Indirect costs of care

8. Quality of life

- 8.1 Significant important change in quality of life, as defined by each of the studies
- 8.2 Average endpoint of change score in quality of life

9. Satisfaction with care/treatment for either recipients of care or carers

- 9.1 Significant important change in satisfaction with care/treatment, as defined by each of the studies
- 9.2 Average endpoint of change score in satisfaction with care/treatment

'Summary of findings' table/s

We will use the GRADE approach to interpret findings ([Schünemann 2008](#)); and will use GRADE profiler ([GRADEPRO](#)) to import data from RevMan 5 ([Review Manager](#)) to create 'Summary of findings' table/s. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient care and decision making. We aim to select the following main outcomes for inclusion in the 'Summary of findings' table/s:

- Mental state: Clinically important response - psychotic symptoms
- Mental state: Clinically important response - affective symptoms
- Service utilisation: Hospital admission, re-admission or both
- Leaving the study early
- Adverse events: Any significant adverse effects

- Economic outcomes
- Quality of life

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Trials Register

The Trials Search Co-ordinator (TSC) will search the Cochrane Schizophrenia Group's Study-Based Register of Trials using the following search strategy:

Clozapine in Intervention of STUDY

In such study-based registers, searching the major concept retrieves all the relevant keywords and studies because all the studies have already been organised based on their interventions and linked to the relevant topics.

The Cochrane Schizophrenia Group's Register of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, EMBASE, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, hand-searches, grey literature, and conference proceedings (see [Group Module](#)). There are no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We will inspect references of all included studies for further relevant studies.

2. Personal contact

We will contact the first author of each included study for information regarding unpublished trials. We will note the outcome of this contact in the tables of 'Characteristics of included studies' or 'Characteristics of studies awaiting classification'.

Data collection and analysis

Selection of studies

JL and JT will independently inspect citations from the searches and identify relevant abstracts. JM will re-inspect a random 20% sample to ensure reliability. Where disputes arise, we will acquire the full report for more detailed scrutiny. JL and JT will obtain

and inspect full reports of the abstracts meeting the review criteria. Again, JM will re-inspect a random 20% of reports in order to ensure reliable selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review authors JL and JT will extract data from all included studies. In addition, to ensure reliability, JM will independently extract data from a random sample of these studies, comprising 10% of the total. Again, we will discuss and document any disagreement and, if necessary, we will contact authors of studies for clarification. We will attempt to extract data presented only in graphs and figures whenever possible, but will include only if two reviewers independently have the same result. We will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies are multi-centre, where possible we will extract data relevant to each component centre separately.

2. Management

2.1 Forms

We will extract data onto standard, simple forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:

- a) the psychometric properties of the measuring instrument have been described in a peer-reviewed journal ([Marshall 2000](#)); and
- b) the measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally the measuring instrument should either be i. a self-report or ii. completed by an independent rater (not the therapist). We realise that this is not often reported clearly; in 'Description of studies' we will note if this is the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult-to-measure conditions such as schizophrenia. We have decided to primarily use endpoint data, and only use

change data if the former are not available. If appropriate we will combine endpoint and change data in the analysis as we aim to use mean differences (MD) rather than standardised mean differences throughout (Higgins 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aim to apply the following standards:

For large studies and change data:

We will use data from studies of at least 200 participants, for example, in the analysis irrespective of the following rules, because skewed data pose less of a problem in large studies. We will also enter change data as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We will present and enter change data into statistical analyses.

For endpoint data from smaller studies (under 200 participants):

(a) when a scale starts from the nite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation. If this value is lower than 1, it strongly suggests a skew and we will exclude these data. If this ratio is higher than 1 but below 2, there is suggestion of skew. We will enter such data and test whether its inclusion or exclusion would change the results substantially. Finally, if the ratio is larger than 2 we will include these data, because skew is less likely (Altman 1996; Higgins 2011).

b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), (Kay 1986) which can have values from 30 to 210), we will modify the calculation described above to take the scale starting point into account. In these cases skew is present if $2\text{ SD} > (S - S_{\min})$, where S is the mean score and ' S_{\min} ' is the minimum score.

2.5 Common measure

To facilitate comparison between trials, we intend, where possible, to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we will make efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 20% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht

2005). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we will enter data in such a way that the area to the left of the line of no effect indicates a favourable outcome for pharmacological augmentation of clozapine. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved') we will report data where the left of the line indicates an unfavourable outcome and make a note in the relevant graphs.

Assessment of risk of bias in included studies

Again review authors JL and JT will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagree, we will make the final rating by consensus, with the involvement of JM. Where inadequate details of randomisation and other characteristics of trials are provided, we will contact authors of the studies in order to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise as to which category a trial is to be allocated, again we will resolve by discussion.

We will note the level of risk of bias in the text of the review, Summary figures, and in the 'Summary of findings' table/s.

Measures of treatment effect

1. Binary data

For binary outcomes we will calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive than odds ratios (Boissel 1999); and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). The number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) with their confidence intervals are intuitively attractive to clinicians but are problematic both in accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' table/s we will, where possible, calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes we will estimate mean difference (MD) between groups. We prefer not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity are used, we will presume there is a small difference in measurement, and we will calculate effect size and transform the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

- Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will contact first authors of studies to attempt to obtain intra-class correlation coefficients for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

- Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect. We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) [Design effect = $1 + (m - 1) \times \text{ICC}$] (Donner 2002). If the ICC is not reported we will assume it to be 0.1 (Ukoumunne 1999). If cluster studies have been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002).

As both effects are very likely in severe mental illness, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary we will simply add and combine within the two-by-two table. If data are continuous we will combine data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where the additional treatment arms are not relevant, we will not use these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We choose that, for any particular outcome, should more than 50% of data be unaccounted for, we will not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study are lost, but the total loss is less than 50%, we will address this within the 'Summary of findings' table/s by down-rating quality. Finally, we will also downgrade quality within the 'Summary of findings' table/s should loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 50% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes the rate of those who stay in the study - in that particular arm of the trial - will be used for those who did not. We will undertake a sensitivity analysis testing how prone the primary outcomes are to change when data only from people who complete the study to that point are compared to the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

We will use data where attrition for a continuous outcome is between 0% and 50%, and data only from people who complete the study to that point are reported.

3.2 Standard deviations

If standard deviations are not reported, we will first try to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error and confidence intervals available for group means, and either P value or 't' value available for differences in mean, we can calculate them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): When only the standard error (SE) is reported, standard deviations (SDs) are calculated by the formula $SD = SE * \sqrt{n}$. Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics (Higgins 2011). If these formula do not apply, we will calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We nevertheless will examine the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We will therefore not exclude studies based on the statistical approach used. However, we will preferably use the more sophisticated approaches (e.g. MMRM or multiple-imputation rather than LOCF) and we will only present completer analyses if some kind of ITT data are not available at all. Moreover, we will address this issue in the item "incomplete outcome data" of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply inspect all studies for clearly outlying people or situations which we had not predicted would arise and discuss.

2. Methodological heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods which we had not predicted would arise and discuss.

3. Statistical heterogeneity

3.1 Visual inspection

We will visually inspect graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I² statistic

We will investigate heterogeneity between studies by considering the I² method alongside the Chi² P value. The I² provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I² depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi² test, or a confidence interval for I²). We will interpret an I² estimate greater than or equal to around 50% accompanied by a statistically significant Chi² statistic as evidence of substantial levels of heterogeneity (see section 9.5.2 of *Cochrane Handbook for Systematic Reviews of Interventions* - Higgins 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

1. Protocol versus full study

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will try to locate protocols of included randomised trials. If the protocol is available, we will compare outcomes in the protocol and in the published report. If the protocol is not available, we will compare outcomes listed in the Methods section of the trial report with actually reported results.

2. Funnel plot

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are again described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We are aware

that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We will not use funnel plots for outcomes where there are 10 or fewer studies, or where all studies are of similar size. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model: it puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect these studies can either inflate or deflate the effect size. We choose the random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

No subgroup analysis is planned.

1.2 Clinical state, stage or problem

We propose to undertake this review and provide an overview of the effects of pharmacological augmentation of clozapine for people with schizoaffective disorder in general. In addition, however, we will try to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

We will report high inconsistency. First we will investigate whether data have been entered correctly. Second, if data are correct, we will visually inspect the graph and successively remove studies outside of the company of the rest to see if homogeneity is restored. For this review we have decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we will present these data. If not, we will not pool data and will discuss issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state. When unanticipated clinical or methodological heterogeneity are obvious we will simply state hypotheses regarding these for future

reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

We aim to include trials in a sensitivity analysis if they are described in some way as to imply randomisation. For the primary outcomes we will include these studies and if there is no substantive difference when the implied randomised studies are added to those with better description of randomisation, then we will use all relevant data from these studies.

2. Assumptions for lost binary data

Where assumptions have to be made regarding people lost to follow-up (see [Dealing with missing data](#)) we will compare the findings of the primary outcomes when we use our assumption/s and when we use data only from people who complete the study to that point. If there is a substantial difference, we will report results and discuss them but will continue to employ our assumption. Where assumptions have to be made regarding missing SDs data (see [Dealing with missing data](#)), we will compare the findings of the primary outcomes when we use our assumption/s and when we use data only from people who complete the study to that point. A sensitivity analysis will be undertaken testing how prone results are to change when completer-only data only are compared to the imputed data using the above assumption. If there is a substantial difference, we will report results and discuss them but will continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available, allocation concealment, blinding and outcome reporting) for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias does not substantially alter the direction of effect or the precision of the effect estimates, then we will include data from these trials in the analysis.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we use imputed values for ICC in calculating the design effect in cluster randomised trials. If substantial differences are noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we will not pool data from the excluded trials with the other trials contributing to the outcome, but will present them separately.

5. Fixed and random effects

We will synthesise all data using a random-effects model; however, we will also synthesise data for the primary outcome using a fixed-effect model to evaluate whether this alters the significance of the results

ACKNOWLEDGEMENTS

The Cochrane Schizophrenia Group Editorial Base in Nottingham produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

We would like to thank Johannes Schneider and Vivek Agarwal for peer reviewing this protocol.

The search term was developed by the Trial Search Co-ordinator of the Cochrane Schizophrenia Group and the contact author of this protocol.

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- * Indicates the major publication for the study

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John Tully: protocol development

James H MacCabe: protocol development

DECLARATIONS OF INTEREST

John Lally: none known

John Tully: none known

James H MacCabe: none known

SOURCES OF SUPPORT

Internal sources

- Institute of Psychiatry , King's College London, UK.

Salary support provided by the Institute of Psychiatry for all authors

External sources

- No sources of support supplied